

WS2.9 Expression and regulation of IFRD1 in neutrophils of cystic fibrosis patients

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Objectives: Interferon-related development regulator 1 (IFRD1), a protein highly expressed by neutrophils, was identified as a key modifier gene for cystic fibrosis (CF) lung disease in a genome wide association study. The expression levels and regulation of IFRD1 in neutrophils remained elusive. Here we investigated the protein expression and regulation of IFRD1 in peripheral blood and airway neutrophils from CF and healthy subjects.

Methods: IFRD1 expression was measured in peripheral blood and airway neutrophils from CF patients and healthy donors by flow cytometry. Where indicated, isolated neutrophils were stimulated prior to analyses. Isolated DNA from whole blood samples from CF patients were analyzed for *IFRD1* single nucleotide polymorphisms (SNPs). Longitudinal lung function data and IFRD1 expression / regulation were correlated with *IFRD1* SNPs.

Results: Peripheral blood neutrophils from CF patients expressed higher protein levels of IFRD1 compared to peripheral blood neutrophils from healthy subjects. In CF patients, IFRD1 protein levels in neutrophils were decreased in airway fluids compared to peripheral blood. *In vitro* studies showed that CXCL8 down-regulated IFRD1 expression in neutrophils, an effect that was abrogated with a CXCR2 inhibitor. Four IFRD1 SNPs modulated lung function in CF patients. Comparing different IFRD1 alleles showed that CXCL8 regulated IFRD1 expression depending on the genotype.

Conclusions: These studies demonstrate that

- i. IFRD1 protein expression is upregulated in peripheral blood but not in airway CF neutrophils and
- ii. CXCL8 modulates IFRD1 expression depending on the IFRD1 genotype.